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## REPORT ON SCIENTIFIC MEETING

# Gender identity disorder in adolescents<sup>☆,☆☆</sup>

H. Asscheman (MD, PhD)<sup>1</sup>

Valeriusstraat 4hs, 1071 MH Amsterdam, Netherlands

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### KEYWORDS

Gender identity disorder;  
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 Puberty-delaying treatment

**Summary** At a recent conference in London the problems and possibilities of clinical management in gender identity disorder (GID) of adolescents were addressed. The number of referrals of adolescents with GID has tripled in recent years. With the uncertainties of the DSM classification and the lack of reliable criteria diagnosis remains controversial. Atypical gender behaviour is rather common in children but persistent GID in adolescence is only seen in 25% of the referred children. The role of pubertal hormones in brain development is the subject of studies but no clear answers are (yet) available. Prenatal hormone exposure is clearly linked to child play behaviour but does not appear to be the most important factor for gender identity. An option for adolescents with persistent GID and an increase of distress at puberty is puberty-delaying treatment with GnRH analogues. This treatment relieves distress and no detrimental physical effects have been observed, but follow up is limited. From an ethical point of view, the developing autonomy of the adolescent with GID should receive more attention and a practical approach should underscore the experimental nature of the intervention and the possibility of withdrawal from treatment. In dealing with adolescents with GID puberty-delaying treatment is a valuable option with encouraging preliminary results, but long term outcome studies and more research are necessary.

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Gender identity disorder, often used synonymously with gender dysphoria, or in its most extreme form transsexualism may arise in childhood. The feeling of belonging to the other sex can be transient, particularly in prepubertal children, or presage a state of permanent discomfort with the anatomical sex requiring medical and psychological intervention.

Adolescence can be very distressing. for these young people and decision-making with regard to clinical management is very complex. In this meeting a number of world-renowned experts shared their experience, knowledge and opinions in addressing the problem of gender identity disorder in adolescents.

Professor Kenneth Zucker, head of the gender identity service in the Child, Youth and Family Program at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, spoke on definition and spectrum of gender identity disorder.

Research on adolescents with gender identity disorder (GID) has lagged behind corresponding research on both children and adults with GID. At the gen-

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E-mail address: [h.ajap@worldonline.nl](mailto:h.ajap@worldonline.nl).

<sup>1</sup> Internist-endocrinologist.

der identity service in Toronto, the number of referred adolescents/year has tripled since 2004 from the preceding 30 years.

The definition of GID before adulthood is difficult as appears from the different diagnostic categories in the DSM classifications. DSM-III had gender identity disorder of childhood and transsexualism in adolescents/adults and DSM-III-R had a new diagnosis, Gender Identity Disorder of Adolescence and Adulthood, Non-Transsexual type, but this diagnosis was deleted from DSM-IV. In DSM-IV-TR, GID was developed with different criteria sets for children vs. adolescents/adults. Currently, a new revision of DSM is discussed (prof. Zucker is the Chair of the DSM-V Workgroup on Sexual and Gender Identity Disorders and prof. Cohen-Kettenis is the Sub workgroup Chair for GID). Philosophically, the first question is: should GID be in the DSM?, implying it is a mental disease. But if not a mental disease, what is it? Maybe it is better to speak about gender dysphoria as a descriptive term and transsexualism as the most extreme form. Most clinicians make the diagnosis empirically, but this lacks reliability and there is no consensus on a single or number of criteria or period of time.

Questionnaires are used to help diagnosing GID. There are also other measures of behaviour problems, but it is unclear what the relation is between these problems and the diagnosis of GID. Are behaviour problems causal, unrelated, secondary to or a part of the GID? With the increasing numbers of adolescents referred to specialized centres, it has become even more important to develop standardized diagnostic and assessment protocols for adolescents, which can be used as baseline data in the evaluation of therapeutic interventions.

More than simply looking at symptoms, a dimensional approach (to which degree) is warranted.

The second presentation by doctor Dave King, senior lecturer in Sociology, University of Liverpool and co-author of *The Transgender Phenomenon* (2006), explored within a sociological framework the historic background of gender dysphoria. He used "entitlement" as the theme that runs throughout this history. Entitlement relates to: 1. the extent to which legitimacy is accorded the claims by the medical profession; 2. the extent to which legitimacy is accorded to various medical and other interventions and on what grounds; 3. the extent to which legitimacy is accorded socially and legally. Starting with Christine Jorgensen he explored the changing conceptualisations and nomenclature in the field, from the coining of the term "transsexuals" by Magnus Hirshfeld to the often controversial developments of endocrinology and surgery that made it possible to alter the sex characteristics of the body.

Unfortunately, lack of time prevented him from discussing the actual situation in the UK.

Professor Peggy Cohen-Kettenis (professor of medical psychology and director of the centre of expertise on gender dysphoria at the VU University Medical Center, Amsterdam) started her talk on epidemiology and natural history by stating that formal studies on GID in individuals of all ages are lacking.

Gender atypical behaviour is rather common in children. Epidemiological data in the Netherlands from studies with the Child Behaviour Checklist (CBCL), a questionnaire filled out by parents, indicate that 5% of girls and 2,6% of boys

between 4 and 11 years show behaviour of the opposite sex as judged by their parents. In adolescents 2% of girls and 1,1% of boys show this behaviour. However, few children are referred for evaluation and advice, suggesting that many parents are not seriously concerned by this behaviour, but the numbers slowly increase: 35 children (4–11 years old) per year in the Netherlands (M/F 2.93). In adolescents the number of referrals in the Netherlands has increased steeply to 30–35 per year with a Male/Female ratio of 1.2:1. Sex ratios of referred adolescents with GID in Canada (1.5:1) and the UK (1.4:1) also show that in adolescence GID is almost as common in girls as in boys. This is in strong contrast with GID in referred children where boys outnumber girls 3 to 5 times in all reported studies. Probably a Tommy boy is less a problem than a Sissy boy for many parents of younger children, reflecting a different referral pattern.

A number of studies have reported follow up and outcome of children with GID. All studies have relatively small numbers ( $n=25-77$ ), different inclusion criteria and probably referral patterns. Some studies have shown that GID persists in 7–12% of referred children but the more recent and larger studies report 25–27% of persistent GID after adolescence. Larger percentages of children with GID are reported to become homo- or bisexual (33 to 75%) but still a considerable number become heterosexuals without gender identity problems. The outcome studies underscore that GID in children is not comparable to (and does not reliably predict) GID in adults and, therefore, needs a different therapeutic approach. Good outcome studies on adolescents with GID are lacking but clinical experience suggest that persistent GID is very common, in particular in the more extreme forms of gender dysphoria.

Professor Sarah-Jayne Blakemore and her research group from the Institute of Cognitive Neuroscience (University College London) use a variety of behavioural and neuroimaging methods to study the development of mentalising, action understanding and executive functioning during adolescence. Brain development is a continuing process after birth. In animals the development of the brain appears completed at 3 years of age. In humans the process takes much longer and in adolescence with its physical and hormonal changes, an important developments take place. Little difference in brain development between boys and girls has been reported but most studies have not looked closely into sex differences. Research in humans has shown that the visual cortex develops up into childhood (until 3 years), but the (pre)frontal areas develop later with an increase at puberty and peak (in girls at 11 and in boys at 13 years of age) and a further decrease (up to 22 years of age). During puberty the total volume of brain tissue remains the same but there is an increase in myelination (which increases transmission speed) and there is a gradual decrease in synaptic density, indicating significant "pruning" of connections.

The mediofrontal cortex is considered as the "social brain" At the age of 5 children already have social understanding of emotions, attribution to other people but this is at a direct basal level, and only around 14 they understand intention (e.g. irony) and consequences. In a number of studies with functional MRI adults show less activation in the prefrontal area with tasks that demand understanding intention and irony compared to adolescents. Why there is more activation ("storm in the brain") in adolescents

is unclear. Do adolescents use a different strategy or do they have a less efficient brain (more synapses and more activation)?

At the moment there are many questions and sex differences have hardly been researched.

Endocrine influences on the development of gender identity was the subject of professor Melissa Hines from the Department of social and developmental psychology at the University of Cambridge, UK. Theories on gender identity development can be divided into inborn: genetics and prenatal hormones, and postnatal: socialisation and wrong cognition models.

The famous case of John who lost his penis at 17 months of age in accidental burn during circumcision, was raised as Joan on the advice of John Money and returned later to live as John and committing suicide many years later, is often used as proof for an inborn gender identity. However, similar cases of boys losing their penises soon after birth have shown that raising as a girl may have a good outcome as a happy woman.

The simple model of genes that develop the testis and the production of hormones that are all decisive is too simple. Hormones have two effects, the activational, the transit to adulthood and an organisational effect, often prenatally, that leads to a permanent modification of the brain. This organisational effect on the brain is well known from rat experiments in which one injection of testosterone in female rats after birth is followed by a mounting (male sexual) behaviour in adulthood. Just one injection of testosterone in the right period is sufficient to change their sexual behaviour to a male pattern in adulthood due to a permanent brain modification. In rodents this is not caused by testosterone but by oestradiol produced by local aromatisation of testosterone. Administration of DES to pregnant rodents increases the mounting (male) behaviour in females but causes also earlier lordotic (female) behaviour. At least in rodents, hormones appear to have two different (opposite) sexual behavioural effects. In rats and rhesus monkeys sex hormones during brain development influence also other non-sexual behaviour. The explanation might be as we have learned from animal experiments, that oestradiol increases growth of dendrites, prevents apoptosis and has other effects in parts of the brain that contain the appropriate receptors.

The knowledge in humans comes from studies in patients with disorders of sexual development (DSD). Many studies in girls with congenital adrenal hyperplasia (CAH) have shown a preference for boy toys and activities compared to reference girls. However, only 2–5% of the CAH girls who have been raised as females show gender identity disorder to the extent that they choose to live as men.

In 5 $\alpha$ -reductase deficiency, boys are born with underdeveloped genitals and often raised as girls. At puberty their genitals virilize and originally it was reported that they reverted to the man's role. This occurred among the isolated populations (Dominican Republic, New Guinea) where 5 $\alpha$ -reductase deficiency was not uncommon. Nowadays sporadic cases in other populations are diagnosed. In the third world most of these patients still choose to live as men but in the western world only far fewer do so. Is it more advantageous to be a man in developing countries?

In patient with the complete androgen insensitivity syndrome (AIS) GID is unknown, but in partial AIS 9% of those reared female choose to become a man. In patients with testicular agenesis 13%, with cloacal extrophy 22% and with penile ablation 29% choose to live as a man.

In conclusion, hormones alone are not the most important factor for gender identity, but child play behaviour is clearly linked to sex hormone, particularly in CAH girls. It is possible that other factors like Mullerian inhibiting factor (MIF) and other genes, as well as hormones, also play a role.

Dr Domenico Di Ceglie, director of the Gender Identity Development Service (GIDS) at Tavistock & Portman NHS Trust in London, addressed the role of the GIDS within the NHS and its relation with self-help organisations, the assessment process and the therapeutic aims and psycho-social interventions. He discussed the CARE model as used in his clinic and the tension between the professionals and the self help groups. His group focuses on acceptance by their social environment (including school) and broadening the behavioural repertoire of the child and evaluation. After an extensive assessment with many questionnaires, and including the family of course, most support is psychosocial. Only around 16 years of age adolescents are referred for treatment. Self help groups are useful but at times try to dominate the process by insisting on a premature risky course of treatment. In the discussion after his talk the self help groups present refuted this and blamed him for waiting too long time.

Options in endocrine treatment towards a consensus was presented by Dr Russell Viner, Institute of Child Health and professor Henriette Delemarre-van de Waal, Leiden University Medical Center. In 2006 at a previous meeting on gender identity in adolescents the speakers were opponents in a pro-contra debate. This time they presented together, a much appreciated effort towards consensus. Arguments in favour of early treatment, suppressing hormonal puberty, are the reduction of distress and less gender confirming (cosmetic) surgery. Against, the risk of as yet unknown side effects and the possibility of influencing outcome by this treatment. The Dutch approach, puberty suppression at Tanner stage 2 or more, usually 13–15 years in those who have a clear increase in distress by the puberty development and cross-sex hormones at 16, differs from the UK approach, start hormones at the age of 16, in which only a stable gender identity is required and distress is not mentioned.

Professor Delemarre reported on her experience with GnRH analogues in early pubertal adolescents with GID. It resulted in an immediate relieve of distress, measured by a significant amelioration of the Childhood Behaviour Checklist score rated by the patients. Bone density did not change during treatment while in controls it increased with age, but after the start of cross-sex hormones in adolescents with GID BMD z-scores caught up (from -2 to -0.4). It is too early for firm conclusions because few subjects have reached their peak bone mass which is present at the age of 25 years. GnRH agonist-induced pubertal delay put the pubertal growth spurt at a halt but on tailored administration of cross-sex hormones pubertal increase in height showed a catch up similar as found in children with delayed puberty and even allowed the development of an adult height more commensurate with the re-assigned sex (less in male-to-female and more in female-to-male).

In 120 male and female children and adolescents (1 male and 1 female friend for each subject with GID, aged 9–25) data on structural and functional MRI have been collected. First analyses of 50 fMRIs showed cognitive function similar to the desired sex. Detailed analyses including total brain volume, amounts of grey and white matter and CSF will follow. An international study on outcome with the same protocols and questionnaires has started in London, Amsterdam, Boston, Oslo, Toronto and Ghent.

The salutary psychological effects of hormonal intervention in pubertal children with GID are presently clear, and, while studies continue, there have not been reasons to believe that the bodily effects of the intervention are detrimental.

Doctor Vic Larcher, Chair of the Great Ormond Street Hospital Clinical and Ethical Committees (also Ethics Committee of the Royal College of Paediatrics and Child Health) discussed the subject of ethical issues in GID and gender reassignment. Clinicians have the duty to act in the best interest of their patients. For adults the primacy of the obligation to respect autonomy of the patient is widely accepted but in some circumstances (e.g. euthanasia) it is ethical to limit autonomy.

The extent to which adolescents possess the characteristics (mental maturity) that require clinicians to respect their choice over gender identity has been debated as has their capacity to exercise choice over treatment options for gender reassignment. Conversely, the adverse effects of failing to respect developing autonomy are increasingly acknowledged in respect of those adolescents to whom halting of hormonal puberty is not offered. When there is disagreement between professionals and adolescents and their families over the age at which puberty delaying treatment should be offered, a practical approach that underscores the experimental nature of this treatment may be helpful. This approach considers clinical need, scientific basis, professional consensus, holistic assessment of best interest, patient's

understanding of the experimental nature the intervention and the possibility of withdrawal from treatment.

Good ethical decision-making requires that the process is transparent, inclusive, reasonable and accountable. Dr. Larcher used the word compassionate decision-making, rejecting the strict age limit as is the rule now in the UK.

Professor Philip Steer, emeritus professor of Obstetrics, Imperial College London and president of the section O&G of the RSM, spoke on prognosis and follow up. He presented himself as a GID-naïve person. His personal experience with the problems of gender identity is limited to a student elective at the Johns Hopkins Hospital, Baltimore in 1970. At this hospital John Money set up the USA's first gender clinic and the first sexual reassignment surgery in the USA was performed on Philip/Phyllis Wilson. He referred also to the case of John/Joan by his real name David Reimer (as he published his life story), as an example of cases that went wrong. Anecdotally, other case histories from the androgen insensitivity syndrome support group do not make comforting reading. Long term (> 40 years) follow-up data on GID in children and adolescents are sparse in the literature, but both follow-up from childhood to adolescence, and adolescence to young adulthood suggest that more than half, and up to 80%, become homosexual or bisexual. Anecdotal evidence suggests a high proportion of continuing psychological morbidity. Surgical intervention is unlikely to cure psychological problems, and should be reserved for adults.

I had to leave before the following discussion and closing remarks and cannot report these here. In my view the meeting gave a very balanced view of the state of art of treating gender identity disorders in adolescents. Puberty delaying treatment is a valuable option in dealing with adolescents with gender identity disorder if used under conditions and in the context of a protocol. Preliminary results are encouraging and ethically the proposed approach is acceptable, but long term outcome studies and more research are necessary.